Reply: As stated previously half the herds in the Dominion producing below the Dominion average are primarily limited by their plane of nutrition and in herds above the Dominion average breeding becomes increasingly important. If all the dairy cows in the Dominion were on an optimum plane of nutrition we might lift our average production to over 300 lbs. per cow.

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THE RELATION OF THE ENDOCRINE SYSTEM TO REPRODUCTION AND MILK SECRETION

by

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No symposium on lactation and reproduction would be complete without due consideration of hormonal aspects. The chief aim of this paper is therefore to emphasise the fundamental role played by the endocrine system in the processes which form the theme for the initial phase of this conference.

For the purpose of this paper relevant endocrine factors have been divided into four groups: 1. gonadotropic factors, 2. ovarian and testicular factors, 3. mammary growth factors, 4. factors concerned with the initiation and maintenance of lactation.

Gonadotropic Factors: This group may be divided into two classes according to the source of the hormones. There are the gonadotropins of pituitary origine, and those found in the body fluids when living chorionic tissue is present.

The pituitary gonadotropins are concerned chiefly with ovarian follicular growth and luteinization in the female, and stimulation and maintenance of spermatogenesis and the function of the testicular interstitial tissue in the male. Although there is no general agreement as to the number of factors involved or their identity, the majority of workers subscribe to the theory that there are two separate pituitary factors - follicle stimulating hormone (F.S.H.) and luteinizing hormone (L.H.) At present convenient simple biological tests for neither factor are available. To avoid confusing results due to the reaction of the intact test animal's own pituitary hypophysectomized animals must be used in critical work.

It is of interest to consider the properties ascribed to each of the factors. In the hypophysectomized female animal, follicle stimulating hormone is believed to cause growth and development of the follicles, but to have no luteinizing effect. Incidentally, other changes are stimulated through the production of estrogen by the growing follicle. In the hypophysectomized male, F.S.H. maintains or repairs the seminiferous tubules and stimulates the initial phases of sperm formation. Luteinizing hormone alone is claimed to have no growth promoting effect on immature follicles in hypophysectomized females. Where there are follicles fully or partly developed, luteinization will follow the administration of this hormone. L.H. causes growth and functional activity of the interstitial cells of the testes of hypophysectomized animals. There are also indirect effects due to the resulting production of the male sex hormone androgen. If degeneration has not taken place, the seminiferous tubules are maintained, but it has been found that androgens are able to do this alone.

The identity of the two separate factors F.S.H. and L.H. has been questioned. It has been found that by manipulating the rate at which unfractionated gonadotropic material reaches the ovary, the results may be altered; e.g. slow absorption gives only F.S.H. results. Furthermore, the best preparations of F.S.H. or L.H. from pituitary material made thus far, when given in high enough doses, gives effects ascribed to the other factor. Only by the isolation and study of chemically pure pituitary fractions will this controversy be settled finally.

A considerable amount of gonadotropin is found in the urine of castrate individuals or post menopause women. The source of the gonadotropin is the pituitary. This material appears to have the properties of F.S.H. predominately, but if sufficient material is administered to test animals, some L.H. effects may be demonstrated. If test animals are intact, administration of F.S.H. preparations may result in the formation of some corpora lutea due to the reaction of the animal's own pituitary which supplies some L.H., probably in response to the initial follicle stimulation.

It has been shown that the effect on the ovary of administering F.S.H. plus L.H. is greater than the sum of the individual effects of each factor. This phenomenon is called augmentation. It emphasizes the fact that ovarian activity is controlled by a nice balancing of the various hormonal factors involved - a fact which has to be given serious consideration when artificial manipulation of these factors is contemplated.

No pure preparations of pituitary gonadotropins are available on the market at the present time. Commercial preparations have been found to contain considerable amounts of other pituitary factors together with inert proteins.

Gonadotropins appear in the body fluids of certain pregnant animals. Factors found in the urine of pregnant women and in the blood of pregnant mares have attracted much attention, and extracts containing them are of considerable commercial and biological importance. Their significance in the pregnant animal is not well understood, but their properties have been carefully studied because each factor provides a valuable tool for biological work.

The concentration of the gonadotropin found in the urine of pregnant women rises to a peak between 30 and 40 days after conception, and thereafter declines to a low level. The predominating properties of this material appear to be those of a luteinizing factor. Follicle growth is not directly stimulated. In the male animal, the interstitial cells of the testes are activated. This gonadotropin concentration is the basis for the Aschheim-Zondek and Friedman tests for pregnancy in women. In the blood of pregnant mares, especially between the 45 - 95th days of pregnancy there is found a high concentration of gonadotropic material. Extracts of pregnant mare serum have properties which might be expected from a blending of pregnant women's urine and castrate urine. These extracts can stimulate follicular growth, and in some species ovulation also. Positive effects can be obtained on the interstitial tissue and tubules of the testes of a number of experimental animals. Pregnant mare serum appears to be one of the most useful hormonal tools now at the disposal of the physiologist working the field of animal husbandry.

The presence of a high concentration of gonadotropin in the blood of mares 40 - 90 days after service is a reliable sign of pregnancy.

Pituitary gonadotropins, pregnant urine and pregnant mare serum have all been used successfully in stimulating anestrous ovaries in farm animals. The work of Cole (California) and his associates, and of Hammond and his co-workers have been especially notable in this field.

Little progress has been made in the application of these hormonal factors to male reproductive disfunctions. However, it is noteworthy that pregnant womens' urine extracts have been accepted by the American Medical Association Council on Pharmacy and Chemistry with the notation that the only condition in which the human therapeutic response is of value is that of cryptorchism where there is no anatomic abnormality which would prevent testicular descent.

Ovarian and Testicular Factors: This group includes the ovarian hormones estrogen and progestin, and the male sex hormone androgen. The functions of these hormones are too well known to need detailed discussion here. Estrogen induces heat, stimulates the development of the female reproductive tract and mammary glands, and is responsible for the development of the female secondary sexual characters. Progestin induces further development of the uterus and mammary glands, and supresses heat.

It is interesting to note that in some respects estrogen and progestin act synergistically, i.e. the presence of one hormone augments the action of the other. For example this occurs in the development of the uterus and mammary glands. In other cases the action of the two hormones is antagonistic, e.g.estrogen renders the uterine muscle more sensitive, while progestin diminishes the spontaneous contractions and inhibits uterine movement. Estrogen induces heat; progestin in sufficient quantities inhibits heat - e.g. in the pregnant animal large quantities of estrogens are produced but no heat results. However, it has been found that with certain levels of estrogen a regressing corpus luteum is necessary after follicular stimulation before heat is observed. This situation occurs in the case of anestrous ewes injected with pregnant mare serum. Thus in many reactions, the end result observed after the injection of one factor will depend upon the respective concentration of estrogen and progestin in the system.

The male sex hormone, androgen, is secreted by the interstitial cells of the testes under the control of a pituitary gonadotropin. This hormone, as is well known, is responsible for libido in the male, stimulates the development and functioning of the male accessory organs of reproduction, and influences the development of male characteristics. There is good evidence for believing that the rate of androgen secretion is controlled by reciprocal action between the concentration of androgen in the system and pituitary gonadotropin secretion.

Mammary Growth Factors: The influence of the ovarian hormones estrogen and progestin on mammary growth are widely recognised. In general estrogen tends to favour duct growth, and progestin lobule-alveolar development. It is noteworthy that both duct growth and lobulo-alveolar development in intact animals may result from long continued administration of estrogen alone. However, the most rapid and extensive mammary development is stimulated by a certain balanced doseage of estrogen and progestin.

It is perhpas of some practical interest that in experimental animals it has been found that during inanition the effect of estrogen on mammary growth is considerably reduced.

The exact status of the mammogenic pituitary factor or factors is not as well understood. Indeed, the existence of such a factor is still questioned by a few workers. Until it was shown that hypophysectomized animals showed little significant mammary response to the injection of estrogen and progestin, the theory that these hormones acted directly on the mammary gland was not challenged. Since then a considerable amount of evidence has accumulated supporting the view that estrogen and progestin act indirectly on the mammary gland through stimulating the production of a pituitary factor. This latter principle has been called mammogen. By assaying pituitary glands according to the mammary duct growth stimulating properties as tested in male mice, it has been established that pituitary material contains this mammogenic factor in varying concentrations. The concentration of the hormone has been found to be high during the early estrous cycles of heifers and during the first half of pregnancy. These results have fitted well with the known facts of normal mammary development.

The initial work on the chemical nature of the pituitary duct growth factor (mammogen I.) indicated that the hormone was extracted by lipid solvents. This was in sharp contrast to results obtained with other pituitary hormones which have been found to be protein-like in nature. The lipid extract gave no lobule-alveolar development in spayed virgin female mice, but both fresh pregnant cattle pituitaries and protein-extracts gave lobule-alveolar responses. It was therefore postulated that a second factor mammogen II. existed. It was suggested that estrogen stimulated the pituitary to secrete mammogen I. which developed ducts. Estrogen and progestin stimulated the secretion of mammogen II. which developed the lobule-alveolar system.

Since the early work on the lipid nature of mammogen I. has not been confirmed, it seems as well to await further developments in this field before concluding that two mammogenic hormones exist. However, there seems little reason to doubt that during certain periods of rapid mammary growth the anterior pituitary lobe contains a substance or substances which have the ability to stimulate mammary duct and lobule-alveolar development.

Late work has shown that estrogens have a special sensitizing effect on the mammary land, such that it is more responsive to the pituitary mammogenic factors. It has been suggested that estrogen acts thus by increasing the vascularity and permeability of the capillaries of the mammary tissue, allowing a more intensive action by mammogenic hormones.

Summing up the present evidence, it appears that in the normal animal mammogenic factors, estrogen, and progestin in varying relative concentrations bring about normal complete mammary development and provide a gland which will respond with abundant lactation to the appropriate stimulus.

Factors Concerned with the Initiation and Maintenance of Lactation: These factors may be divided arbitrarily into two classes. Firstly there are those hormones which influence the supply of milk precursors to the mammary gland. It is not proposed to deal with these factors in this paper, except to indicate what hormones are involved. Hormonal factors from the thyroid, the adrenal cortex, the pancreas, the parathyroids and the posterior and anterior lobes of the pituitary all exert important controlling influences over metabolites which may be required for the production of milk.

Secondly, the anterior lobe of the pituitary gland secretes a hormone which specifically incites the cells of the mammary alveoli to milk production. This hormone is usually referred to as lactogen. Other names given to the same factor include prolactin, galactin and mammotropin. More advance has been made in the chemical study of lactogen than with any other pituitary hormone. Relatively pure crystalline protein material of high potency has been prepared in several laboratories. As the hormone will stimulate milk secretion in any well developed sensitized mammary gland, this property has been used as an assay procedure. However, the hormone was found to stimulate enlargement of the crop sacs of pigeons with the formation of crop milk, and tests based on this property are almost universally used in assays of the potency of lactogenic material.

Studies of the pituitary glands have shown that the concentration of lactogen is higher in dairy cows than in beef cows, and in lactating cows than heifers. Increased lactogen concentrations following parturition have been demonstrated in the pituitaries of all animals studied. This rise occurs whether or not the glands are suckled. After reaching a peak, concentration declines as lactation proceeds. It has been claimed that nursing or milking plays an important part in stimulating, by a nervous mechanism, the release and further secretion of lactogen by the pituitary.

The hormone estrogen has been shown to stimulate the pituitary to secrete lactogen. There is some evidence that progestin inhibits this action of estrogen. If this is so, the low lactogen content of pituitaries from pregnant animals in which there is normally a high estrogen production could be explained by the fact that there is also at this time a high production of progestin. It has been postulated by Missouri workers that when the production of progestin declines with the approach of parturition, sufficient estrogen remains effective within the system to stimulate the production of lactogen by the pituitary and thus initiate milk secretion. The concentration of lactogen is thereafter kept at a high level by the influence of nursing or milking. Such a theory fits in well with the observation that long continued estrogen treatment may initiate milk secretion.

The foregoing is but a brief survey of hormones involved in reproduction and lactation. It is clear that the efficiency of both processes is dependent not on the action of single hormones acting independently, but on a delicate balancing of the rates of secretion of various endocrine glands.

DISCUSSION.

Professor K.A. Wodzicki: What is the hormone basis of the colostrum production? Is there any relationship between lactogenic, chorionic normally produced hormones, and those found in the urine of men affected with cancer? What is the relationship between hormonic action and the mechanical influence of nursing and milking?

Reply: Although no hormonal basis for colostrum production has been established, it seems possible that the hormone estrogen may have some influence as this hormone is known to increase the permeability of certain tissues. At the Dairy Research Institute a number of dry sterile cows have been injected with stilbestrol in an attempt to induce milk secretion. Two cows receiving high doses of this synthetic estrogen have responded with colostrum secretion only. A cow receiving a lower dose of stilbestrol is now giving 18 - 20 lbs. of normal milk daily.

Nursing or milking stimulation has been shown to influence the endocrine system in at least two ways. Stimulation associated with milking, by means of nervous connections, induces the release of a hormone, probably from the posterior lobe of the pituitary gland, which causes the contraction of fine muscle fibres throughout the mammary gland and thus promotes the discharge of milk. Suckling has also been shown to favourably influence the release and production of the hormone lactogen by the anterior lobe of the pituitary gland.

Professor C.P. McMeekan: Asked what explanation could be advanced for the extraordinary persistence in lactation of the cow in Mr R.A. Candy's herd which had now completed 4 years of continuous milking and each year corresponded to a normal lactation of approximately 600 to 700 lbs. of butterfat.

Reply: A number of cases have been reported of multiparous cows having production records of some magnitude without the normal stimulus of parturition. In each case some ovarian disfunction is involved. It seems likely that the abnormal activity of the ovaries has, in these cases, resulted in the production of hormonal situations similar to those of cows in which milk secretion is normally initiated and maintained at the time of, and after parturition. The excess production of estrogen at some period seems an important feature of these abnormal cases, and it is noteworthy that in experiments animals have been induced to lactate by long continued estrogenic treatment alone. The cow in question is reported by a Morrinsville veterinarian to have an enlarged right ovary, and Mr Candy has indicated that the animal has abnormal heat periods.

Dr C.S.M. Hopkirk: Is there a hormone responsible for the health of seminiferous tubules?

Reply: The efficient functioning of the seminiferous tubules is dependent on a pituitary gonadotropic hormone.

Dr L.R. Richardson: Considering the endocrine system as a balanced controlling mechanism, it is reasonable to expect that interference by any means will produce an antagonistic effect. Is this effect produced, and can Dr Campbell supply information of the appearance of this antagonism in subsequent generations?

Reply: Omitting from this discussion the highly controversial subject of anti-hormones, it is undoubtedly true that disturbance of the normal hormonal balance may have repercussions throughout the endocrine system. For example injection of estrogen may suppress the animal's production of gonadotropin by the anterior pituitary, and render the animal temporarily sterile. Feeding potent thyroid material may depress the activity of the animal's own thyroid. Castration results in a greatly increased production of gonadotropin by the anterior lobe of the pituitary. I do not know of any work, accepted as confirmed, which has shown any carry over of these effects from one generation to another.

Dr P.R.McMahon was interested to see that the phenomena of augmentation, established in the case of interaction among hormones controlling preparation of lactation, gave a factual mechanism or basis for non-additive interactions of genes. Non additive interactions have been suggested from such widely divergent projects as Dry's work on halo hairs and size inheritance in tomatoes. If this is a more general phenomenon than we have expected the practical importance is considerable.

(a) Continued selection is necessary to maintain our present standards.

(b) The upper limit to increased production is extended.

Dr F.W. Dry: In the multifactorial stock of N-type Romney sheep at the Massey College, cited by Dr McMahon, as affording an example of multiplicative or geometric interaction of genetic factors, it is probable that a comparatively small number of pairs of factors multiply one anothers' effects to give enormous numbers of halo hairs. The number of pairs of factors concerned may be as low as three. In this stock, which has been built up by selection gradually, though in a comparatively short time, we may conclude that all the factors operating give very many more halo hairs than a full complement less one. It is likely too, that these factors are dominant, that is a single dose of each suffices to produce full effect.

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